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Direct-acting Oral Anticoagulants
Drug Effectiveness Review Project Summary Report

Date of Review: July 2016 **Date of Last Review:** May 2015

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. What is the evidence on the effectiveness and harms of the novel direct-acting oral anticoagulants (DOACs) compared with each other or with other anticoagulants for treatment of a venous thromboembolic (VTE) event in adults?
2. What is the evidence on the effectiveness and harms of the DOACs compared with each other or with other anticoagulants for extended treatment to prevent recurrence of thromboembolic events in adults at increased risk?
3. What is the evidence on the effectiveness and harms of the DOACs compared with each other or with other anticoagulants for prevention of thromboembolic events in adults with atrial fibrillation (AF) or venous thromboembolic events in adults who have undergone orthopedic surgery?
4. What is the evidence on whether there are subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one DOAC is more effective or associated with fewer harms than another DOAC or other anticoagulants?

Conclusions:
- There is insufficient evidence for direct comparisons of DOACs. All DOAC efficacy and safety outcome comparisons were based on indirect data.
- There is low strength of evidence that there were no differences in all-cause mortality risks between the DOACs when used in patients with non-valvular atrial fibrillation (NVAF) and in patients undergoing hip or knee replacement surgery. There was insufficient evidence to develop conclusions on all-cause mortality risk between the DOACs when used for VTE prevention during extended treatment. Mortality was not assessed in DOAC treatment for VTE.
- For the composite outcome of VTE and mortality in orthopedic patients undergoing hip or knee surgery, there is low-strength of evidence that apixaban and rivaroxaban were associated with the lowest risk when compared to once daily dabigatran based on low strength evidence. There is low strength evidence that apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg daily (OR 0.35; 95% CI, 0.13 to 0.91).
- In patients with NVAF there is low strength evidence that edoxaban 30 mg is associated with a higher risk of the composite outcome of stroke or systemic embolism compared to apixaban 5 mg and dabigatran 150 mg (OR 1.38 and OR 1.64, respectively) twice daily. Rivaroxaban 20 mg daily was found to have a higher risk of stroke and systemic embolism than dabigatran twice daily (OR 1.32, 95% CI, 1.01 to 1.74) based on low strength of evidence. Apixaban and edoxaban were associated with the lowest risk of major bleeds overall compared to the other DOACs.
- For the treatment of VTE there were no differences found for DOAC comparisons based on insufficient evidence for the following outcomes: VTE recurrence, DVT and PE. There is low strength of evidence in this population that major bleeding was less with apixaban compared to edoxaban and dabigatran.

- No differences were found in VTE recurrence, all-cause mortality, acute coronary syndrome, or major bleeding when comparing apixaban, rivaroxaban and dabigatran in patients treated for prevention of recurrent VTE for an extended period (insufficient evidence). Apixaban was associated with less major bleeding than rivaroxaban and dabigatran.
- The evidence of superior efficacy or harms in patient subgroups was insufficient, preventing meaningful conclusions.

Recommendations:
- Evidence from the DERP report supports our current PDL and no changes are recommended.
- Recommend to continue access to all DOACs without prior authorization criteria.

Previous Conclusions:
- Canadian Cardiovascular Society Guidelines strongly recommend the DOAs in preference to warfarin, based on high-quality evidence from primary literature and meta-analyses, for patients with NVAF requiring anticoagulation. This recommendation was based on evidence of non-inferiority to warfarin, with similar or less major bleeding and less risk of intracranial hemorrhage. American Academy of Neurology Prevention of Stroke in NVAF and the European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in AF (SPAF) recommends all of the oral anticoagulant options, without preference, for patients with NVAF. These recommendations were based on evidence from phase 3 trials.
- There is moderate strength of evidence of no difference in efficacy between DOAs and standard therapy (enoxaparin and warfarin) in treating VTE, supported by indirect comparisons from four new systematic reviews.
- There is moderate strength of evidence from a meta-analysis of 10 randomized controlled trials (RCT) that patients with mild (n=28,971) and moderate (n=11,722) renal insufficiency and AF, acute DVT or PE, or extended treatment of VTE that the DOAs are non-inferior to conventional anticoagulants with similar or less major bleeding or clinically relevant non-major bleeding (CRNM).
- There is low strength of evidence that LMWH are superior to warfarin and placebo for the primary prophylaxis of VTE in patients with cancer.
- Low strength of evidence demonstrated that DOA use in patients with VTE and cancer reduced the incidence of recurrent VTE and major bleeding when compared to conventional treatment of enoxaparin and warfarin.
- There is moderate strength of evidence that edoxaban 60 mg daily and 30 mg daily are non-inferior to warfarin for the prevention of strokes and systemic embolism in patients with NVAF. There is moderate strength of evidence, based on one good quality trial, that edoxaban 60 mg daily is non-inferior to warfarin for the treatment of VTE. Edoxaban is not recommended for patients with a CrCl >95 mL/min due to enhanced renal clearance, resulting in reduced efficacy in this population.
- Common adverse reactions (≥1%) seen with edoxaban are: bleeding, anemia, rash and abnormal liver function tests. There is moderate strength of evidence that both doses of edoxaban were associated with significantly less major bleeding and intracranial bleeds than warfarin in patients with NVAF and significantly more gastrointestinal (GI) bleeds in the high dose edoxaban group compared to warfarin.

Previous Recommendations:
- Atrial Fibrillation: Recommend removing the PA requirement for the DOAs, which are currently not preferred. Recommend all DOAs equally as an option for patients with NVAF and consider comparative pricing in executive session.
- VTE treatment: Recommend that all DOAs as options for the treatment of VTE and consider comparative pricing in executive session.
- Orthopedic Prophylaxis: Recommend all DOAs approved for orthopedic prophylaxis as options and consider comparative pricing in executive session.

Methods:
The May 2016 Drug Class Review on newer oral anticoagulants by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
A 2016 DERP summary of DOACs identified 53 good or fair quality studies which compared the DOACs to placebo, warfarin, heparins, or aspirin. Forty-four were randomized controlled trials, 4 were observational studies and 5 were systematic reviews. Table 1 identifies the drugs included in the review. All DOAC comparison were indirect due to lack of direct comparative evidence.

Table 1.0 Anticoagulants Included in the DERP Review

Generic Name	Trade Name	Formulation
Dabigatran	Pradaxa®	Oral capsule
Apixaban	Eliquis®	Oral tablet
Rivaroxaban	Xarelto®	Oral tablet
Edoxaban	Savaysa™	Oral tablet

Effectiveness/Efficacy and Safety of DOACs:

Venous Thromboembolism

- A meta-analysis of six randomized trials found no differences in the DOACs for the outcomes of VTE recurrence, DVT, and PE for the following indirect comparisons (trials directly compared DOAC to LMWH and warfarin) based on insufficient evidence:
  - Edoxaban 30 mg or 60 mg once daily compared to Apixaban 5 mg twice daily
  - Edoxaban 30 mg or 60 mg once daily compared to Rivaroxaban 15 mg twice daily
  - Edoxaban 30 mg or 60 mg once daily compared to Dabigatran 150 mg twice daily
  - Apixaban 5 mg twice daily compared to Rivaroxaban 15 mg twice daily
  - Apixaban 5 mg twice daily compared to Dabigatran 150 mg twice daily
  - Rivaroxaban 15 mg twice daily compared to Dabigatran 150 mg twice daily

- Apixaban 5 mg was associated with less major bleeding than edoxaban 30 or 60 mg once daily (HR 0.37; 95% CI, 0.15 to 0.89) and dabigatran 150 mg twice daily (HR 0.42; 95% CI, 0.17 to 0.99).

- An indirect comparison of data from 3 trials studying extended treatment of VTE prevention, which included the drugs apixaban, dabigatran and rivaroxaban, found no differences for the outcomes of VTE recurrence, all-cause mortality, acute coronary syndrome or major bleeding, based on insufficient evidence.
- This analysis also found apixaban 2.5 mg and 5 mg twice daily to be associated with less clinically relevant non-major bleeding compared to rivaroxaban 20 mg daily (OR 0.23; 95% CI, 0.08 to 0.62 and OR 0.31; 95% CI) and apixaban 2.5 mg daily compared to dabigatran 150 mg twice daily (OR 0.40; 95% CI, 0.17 to 0.97).

Non-Valvular Atrial Fibrillation

- A meta-analysis of 10 trials indirectly comparing the DOACs when used for non-valvular atrial fibrillation (NVAF) (from trial data of DOACs vs warfarin) found no differences in all-cause mortality risk.
- For the composite outcomes of stroke or systemic embolism (SE) edoxaban 30 mg was found to have a higher risk than apixaban 5 mg (OR 1.38; 95% CI 1.07 to 1.80), rivaroxaban 15 mg (OR 2.24, 95% CI 1.07 to 4.93) or dabigatran 150 mg twice daily (OR 1.64; 95% CI 1.23 to 2.20).
- Rivaroxaban 20 mg was associated with a higher risk of stroke or SE compared to dabigatran 150 mg twice daily (OR 1.32; 95% CI, 1.01 to 1.74) with significant differences found in hemorrhagic stroke favoring dabigatran (OR 2.45; 95% CI 1.05 to 5.17).
- All DOACs had a lower risk of stroke or systemic embolism compared to warfarin.
- The risk of myocardial infarction (MI) was lower with rivaroxaban 20 mg, apixaban 5 mg, and edoxaban 60 mg compared to dabigatran 150 mg. Apixaban 5 mg and rivaroxaban 20 mg also had a lower risk than dabigatran 110 mg.
- Edoxaban 30 mg was associated with a higher risk of MI compared to edoxaban 60 mg (1.27; 95% CI, 1.01 to 1.60).
- Intracranial hemorrhage was higher with rivaroxaban 20 mg compared to dabigatran 110 mg and edoxaban 30 mg had a lower risk than rivaroxaban 20 mg. Apixaban 5 mg had less risk of intracranial hemorrhage than dabigatran 150 mg.
- Gastrointestinal (GI) bleeding risk was lower with edoxaban 30 mg compared to both doses of dabigatran and rivaroxaban 20 mg. Risk of GI bleeds were higher with rivaroxaban compared to apixaban and higher with edoxaban 60 mg compared to edoxaban 30 mg.
- Apixaban 5 mg was associated with less major bleeding than dabigatran 150 mg and rivaroxaban 20 mg, however, edoxaban 30 mg had a lower risk than apixaban 5 mg, both doses of dabigatran and rivaroxaban.
- Major bleeds were less with edoxaban 60 mg compared to rivaroxaban 20 mg.
- Rivaroxaban 20 mg had a higher risk of major bleeds than dabigatran 110 mg.
- Edoxaban 30 mg had 41% lower risk of major bleeds than edoxaban 60 mg (OR 0.59; 95% CI, 0.50 to 0.69).
- All DOACs were associated with less risk of major bleeding than warfarin, except rivaroxaban 20 mg. In a sensitivity analysis rivaroxaban 20 mg was found to have an equivalent bleeding risk to warfarin.

Orthopedic Surgery

- Twenty-one orthopedic surgery trials indirectly compared the DOACs to heparins and warfarin.
- For the composite outcome of VTE and all-cause mortality in patients undergoing hip surgery apixaban 2.5 mg twice daily was found to have a lower risk compared to dabigatran 150 mg once daily (OR 0.28; 95% CI, 0.08 to 0.94).
- Rivaroxaban 10 mg twice daily was found to have a lower risk of VTE and all-cause mortality in hip surgery patients compared to dabigatran 150 mg once daily and dabigatran 220 mg once daily (OR 0.30 and 0.43, respectively).
- In patients undergoing knee surgery, apixaban 2.5 mg once daily was superior to dabigatran 150 mg once daily for VTE and all-cause mortality and rivaroxaban 10 mg once daily was superior to dabigatran 150 mg once daily and 220 mg once daily.

- In knee surgery patients apixaban 2.5 mg twice daily was associated with less major bleeding than rivaroxaban 10 mg once daily.
- There was insufficient evidence to determine differences in the all-cause mortality and symptomatic DVT rates between the DOACs.

Subgroup Analysis of DOACs

- All evidence for subgroup comparisons came from indirect data.
- In the treatment of VTE, the history of presence of cancer did not change efficacy or bleeding outcomes.
- Aspirin and non-steroidal anti-inflammatory use increased risk of clinically relevant bleeding with rivaroxaban or enoxaparin use.
- Age or Asian ethnicity had no effect on outcomes when used in patients with AF and taking rivaroxaban, dabigatran or apixaban.
- Use of dabigatran 110 mg and dabigatran 150 mg in patients with AF and diabetes demonstrated superior efficacy for the primary outcome of stroke or systemic embolism compared to warfarin but absolute risk reductions were small (0.54% and 0.38%, respectively).
- No efficacy differences between dabigatran, rivaroxaban or apixaban were found in patients with AF who also had the following comorbidities: heart failure, hypertension, or coronary artery disease.
- In patients with mild to moderate renal dysfunction, no differences were seen in outcomes in patients being treated for AF taking rivaroxaban, dabigatran or apixaban. Patients taking warfarin on hemodialysis were found to have less risk of hospitalization or death due to bleeding compared to rivaroxaban or dabigatran based on observational data.
- Patients with AF taking dabigatran 150 mg and antiplatelet drugs experienced a higher risk of stroke or systemic embolism and major bleeds.

New Safety Alerts:
No new safety alerts identified.

New Formulations or Indications:
In November of 2015, the FDA approved dabigatran (Pradaxa®) for prophylaxis of DVT and PE in patients who have undergone hip replacement surgery. The approval for the added indication came from evidence from 2 randomized, double-blind, non-inferiority trials in 5428 patients. Patients received dabigatran 75 mg orally 1-4 hours after surgery followed by 150 mg daily or 110 mg 1-4 hours after surgery followed by 220 mg daily or enoxaparin 40 mg subcutaneously once daily initiated the evening before surgery. Venous thromboembolism was confirmed by bilateral venography of the lower extremities. Dabigatran 110 mg given 1-4 hours after surgery and followed by 220 mg daily was found to be non-inferior to enoxaparin for the endpoint of VTE and all cause death.

Reference: Pradaxa® (dabigatran) [product information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc., November 2015.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ELIQUIS	APIXABAN	Y
ORAL	CAPSULE	PRADAXA	DABIGATRAN ETEXILATE MESYLATE	Y
ORAL	TABLET	SAVAYSA	EDOXABAN TOSYLATE	Y
ORAL	TABLET	XARELTO	RIVAROXABAN	Y
ORAL	TAB DS PK	XARELTO	RIVAROXABAN	Y
ORAL	TABLET	COUMADIN	WARFARIN SODIUM	Y
ORAL	TABLET	JANTOVEN	WARFARIN SODIUM	Y
ORAL	TABLET	WARFARIN SODIUM	WARFARIN SODIUM	Y